	PL NUMBER: PL 00025/0323
ASSESSMENT REPORT OF PAEDIATRIC DATA	**PRODUCT NAME:** **Trusopt 2% Eye drops solution**
LICENCE HOLDER: **MERCK SHARP & DOHME LIMITED**	**THERAPEUTIC CLASSIFICATION:** **ATC code S01 EC03** **Topical anti-glaucomatous agent carbonic anhydrase inhibitor** **MEETING: 8 February 2005**
ACTIVE INGREDIENT: DORZOLAMIDE HCL OPHTHALMIC SOLUTION 2%)	**PAEDIATRIC MEDICINES WORKING GROUP OF COMMITTEE ON SAFETY OF MEDICINES**
LEGAL STATUS: **POM**	

ASSESSMENT REPORT OF PAEDIATRIC DATA TRUSOPT (DORZOLAMIDE HCL OPHTHALMIC SOLUTION 2%)

Executive summary

Product	TRUSOPT (DORZOLAMIDE HCL OPHTHALMIC SOLUTION 2%)
Mechanism	Topical carbonic anhydrase II inhibitor
Indication	Monotherapy or adjunctive therapy in paediatric glaucoma
Data	1: MAH RDB clinical trial 3 months in 83 patients < 2 yrs old and 101 patients 2 to < 6 years comparing dorzolamide 2% T.I.D. to timolol gel Q.D. in patients with ocular hypertension or glaucoma 2: Non MAH trial 3 months, adjunctive treatment of dorzolamide 2% T.I.D. vs brimonidine tartrate 0.2% T.I.D. in 76 glaucoma patients aged 2 to 7 years inclusive. 3.: Spontaneous reports of adverse reactions
Results efficacy	Topical dorzolamide 2% T.I.D. monotherapy appears to lower IOP by 8 to 9 mmHg compared to baseline in paediatric patients with glaucoma or ocular hypertension in short term clinical studies. However a high percentage of patients, (which appears greater in the age group under 2 years compared to those aged 2 to < 6 years: 47% Vs. 33% respectively), were not considered by clinical judgement to be adequately controlled in terms of IOP. Adjunctive treatment of topical dorzolamide 2% T.I.D. in combination with topical beta-blocker therapy appears to lower IOP in patients with paediatric glaucoma aged 2 to 6 years, by an additional 5mmHg in short term studies where at least 75% were considered at least minimally successful. Longer term efficacy studies (> 12 weeks) are not available.
Results safety	Clinical studies in a limited number of paediatric patients indicated that the majority of adverse reactions were local and non serious. The upper 95% confidence limit for discontinuations attributable to dorzolamide was <11% regardless of age cohort and was associated with local ocular reactions of eye pain, burning or itching. Approximately 26% of patients were observed to experience drug related adverse effects, the majority of which were local, non serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4%, were observed to have corneal oedema or haze. Local reactions appeared similar in frequency to comparator. These studies were not large enough to detect rare adverse reactions. There is a signal from spontaneous reports of metabolic acidosis in the very young.
Conclusions	The product information should be updated to reflect conclusions of efficacy and safety as above. In particular, there are data to support use of topical dorzolamide 2% as adjunctive therapy to beta-blockers in paediatric glaucomas, although the dose used was T.I.D. (adult dose is B.D.) The adult indication for dorzolamide is for monotherapy *as second line* in patients unresponsive to beta-blockers or in whom beta-blockers are contra-indicated in the treatment of ocular hypertension, open angle glaucoma and pseudo-exfoliative glaucoma. With regard to monotherapy in children, it could be argued that the data in children at least support monotherapy as second line, and may justify use as first line monotherapy in the short-term topical treatment of ocular hypertension or glaucoma with dorzolamide 2% in the paediatric population. There should be a contra-indication in those < 36 weeks gestational age and < 1 week of age or with significant renal tubular immaturity.

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1 Introduction

The forthcoming EU legislation on medicines for paediatric use will not be finalised before 2006. In the mean time the MHRA has identified a number of actions to enable progress in this area through the current regulatory framework. One of these actions is to formally request completed paediatric study data from companies, where this is known to exist.
In this context, the MHRA contacted companies whose products appear on the US Food and Drug Administration (FDA) Paediatric exclusivity granted list[1]. This is a list of active substances (with relevant sponsors) for which the FDA has granted data exclusivity in return for the submission of paediatric studies carried out in compliance with an FDA written request. The MHRA only contacted the companies that have not already submitted the data to the UK (or to the European Medicines Agency [EMEA] in the case of a centralised marketing authorisation).

The MHRA contacted Merck Sharp and Dohme (MSD) on 4 May 2004 requesting the submission of all completed paediatric trial data on Trusopt (dorzolamide) as well as a cumulative review of safety. Dorzolamide is a potent inhibitor of carbonic anhydrase II and is indicated in adjunctive therapy or second line monotherapy in ocular hypertension, open angle glaucoma and pseudo-exfoliative glaucoma in adults.

1.1 Dorzolamide and FDA paediatric exclusivity

The FDA public assessment report concluded that the clinical study supported use of dorzolamide 2% in the paediatric population and that the benefits outweighed the risk in the treatment of elevated intraocular pressure in paediatric patients. The proposed indication was recommended for approval. The data submitted to the FDA resulted in a labelling change dated 5 Jan 2004 for the indication “reduction in IOP”. The label states that

> “Safety and IOP-lowering effects have been demonstrated in paediatric patients
>
> Adverse event profile was comparable to that seen in adults”

1.2 Marketing Authorisation Holder (MAH) response to MHRA letter

On 30th July 2004, Merck Sharp and Dohme submitted the following:

1) Clinical study report MK –0507
   A three month, double-masked, active treatment controlled, multi-centre study of 2% dorzolamide three times daily (T.I.D.) and of timolol maleate gel once daily (Q.D.) in paediatric patients < 6 years old with elevated intro-ocular pressure or glaucoma
2) A cumulative review of safety of line listings from the company worldwide adverse event database for reports involving use of the product in patients less than 18 years of age.

[1] http://www.fda.gov./cder/pediatric/exgrant.htm

1.3 Background to congenital and juvenile glaucoma

Glaucoma in childhood is a diverse, blinding group of conditions which have one common feature: raised intra-ocular pressure (IOP). The classification is broadly grouped into congenital (primary developmental anomalies present in the drainage angle or secondary to other ocular or other developmental anomalies) and juvenile onset. Treatment is primarily surgical with medical treatments used as an adjunct. Beta-adrenoceptor blockers have remained first line topical therapy when no contraindications, such as asthma, exist. Clinical opinion is that topical carbonic anhydrase inhibitors appear to be less effective than beta-blockers, but safe systemically, although associated with local irritation and are considered useful as an adjunct to beta-blockers or as first line therapy when beta-blockers are contraindicated. Prostaglandins are not considered as effective in childhood glaucoma as in adult glaucoma, but may have a role in some patients with juvenile open angle glaucoma and others with aphakic glaucoma. Alpha-adrenergic agonists, although effective at least in the short-term, are considered to have serious, potential systemic side effects, which demand close observation when used in neonates and young infants.

1.4 Dorzolamide- current indications, UK paediatric labelling and safety issues of note

This section summarises important information in the UK SPC

Dorzolamide is a potent inhibitor of carbonic anhydrase II (CA-II). Carbonic anhydrase is an enzyme found in many tissues, including the eye and exists as a number of isoforms, the most active being CA-II, found primarily in red blood cells. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour production and consequently, intra-ocular pressure.

Dorzolamide in indicated topically

- as adjunctive therapy to beta-blockers,
- as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contra-indicated in the treatment of ocular hypertension, open angle glaucoma and pseudo-exfoliative glaucoma.

The current dose is one drop three times a day in monotherapy and twice a day in adjunctive therapy.

Current UK labelling regarding children states that “safety and effectiveness in children have not been established.” Dorzolamide is a sulphonamide and although administered topically is absorbed systemically and associated with adverse reactions attributable to sulphonamides. Therapy with oral carbonic anhydrase inhibitors, has been associated with urolithiasis as a result of acid base disturbances, especially in patients with a prior history of renal calculi. In adult clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, some of an allergic nature, were reported with chronic use. Other local effects include: burning and stinging, irido-cyclitis, transient myopia, ocular hypotony/choroidal detachment following glaucoma surgery, and corneal oedema/irreversible corneal decompensation in patients with existing chronic corneal defects and/or a history of intra-ocular surgery. Bitter taste and headache have also been reported. Limited

clinical data in overdose are available but symptoms such as somnolence, nausea, dizziness and headache may occur together with electrolyte imbalance and acidosis.

Pharmacokinetic studies in adults indicated that dorzolamide accumulates in red blood cells (RBCs) during chronic dosing as a result of selective binding to CA-II. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug but also inhibits a less active iso-enzyme CA-I. Dorzolamide is primarily excreted unchanged in urine. After dosing end, dorzolamide washes out of RBCs non linearly with rapid decline of the drug initially followed by a slower elimination phase. When given orally to simulate maximum exposure with chronic ocular dosing, steady state was reached within 13 weeks and CA inhibition was less than anticipated to be necessary for pharmacological effects on renal or respiratory function.

2 Assessment of MAH response

2.1 Pharmacokinetics and Pharmacodynamics

No data supplied.

Comment
Choice of dosing regimen was justified by the MAH for monotherapy on the basis of an FDA request. This is the current UK licensed adult topical dose in monotherapy. This represents the maximum unit dose available for assessment in the paediatric population. The need for further exploration of doses will accord with the data on safety and tolerability, from clinical studies as assessed below. The dosing regimen used in the adjunctive therapy study is T.I.D. which is more frequent than that recommended in the UK SPC.

2.2 Clinical Trial Data: Efficacy

2.2.1 Study Design MAH trial dorzolamide vs timolol
A written request from the FDA specified a randomised double blind parallel group study where the primary objective should evaluate safety and clinical response between treatment groups (dorzolamide and timolol maleate gel).

The MAH provided a primary hypothesis as follows: Among paediatric glaucoma patients < 2 years of age, the true proportion of patients who will discontinue therapy due to a drug related adverse experience is $\leq$ 25% when initial treatment is dorzolamide 2% T.I.D. for up to 3 months. This was also stated for the cohort aged 2 to < 6 years. Primary objectives were then the percentage of patients discontinuing therapy for adverse event reasons and based on the upper limit of the exact 95% confidence interval. Secondary objectives were characterisation of IOP, the need for additional therapy and the effect of treatment on total CO_2.

Patients received a baseline pre-study evaluation. The discontinuation of topical or systemic ocular hypotensive therapy was required for 24 hours prior to this.

Eligible patients were randomised in a 2:1 ratio to dorzolamide 2% T.I.D. or timolol once in the morning with separate allocation schedules for patients in each age cohort (<2 year timolol gel **0.25%** mane, 2<6 years: timolol gel **0.5%** mane). Dummy bottles were provided containing placebo to maintain the blinding for administration

schedules. Parents were instructed that administration was to be consistent for the study duration. Parents were requested to report any missed doses on a report form. Compliance was assessed as % actual v possible study doses administered. 50 patients < 2 years of age and 50 patients 2 to < 6 years were required. The study was carried out in 22 US and 13 non US sites.

Study criteria included: IOP ≥ 22mmHg in suspected or confirmed paediatric glaucoma patients and excluded patients such as those with a recent history of glaucoma surgery, trauma, ocular infection or inflammation, renal dysfunction, contra-indications to study therapy or concomitant therapy known to affect IOP. Only 1 eye per patient was randomised in the study.

Patients returned at week one and other scheduled examinations. If IOP was "controlled" (a level suitable for that patient determined by the investigator), then ***masked monotherapy*** was continued. If IOP was not controlled, then therapy was changed to concomitant dorzolamide plus timolol therapy (***open label concomitant phase)***. Patients were discontinued from the study if IOP was uncontrolled one week after the start of concomitant therapy.

Assessments included ocular and medical history, physical examination, alertness assessment, visual acuity, external and anterior ocular examination, IOP measurement, corneal diameter measurement, lens and ophthalmolscopy, patient report card, vital signs, total CO_2 and adverse event monitoring. Investigators were instructed to attempt to make timing of IOP measurement consistent for individual patients and record the time elapsed since study drug administration. Method of IOP measurement was not stated in the study report.

The analysis of the safety outcome was to be based on exact 95% confidence intervals for the proportion of patients discontinuing for possible, probable or definite ADRs by age strata using the "All Patients as treated" (patients with at least one dose of study drug and according to treatment received regardless of randomisation).
IOP efficacy was assessed on the basis of mean change and mean per cent change from baseline up to week 12 using "All patients treated" (patients with baseline and at least one efficacy measurement as randomised, regardless of switching to combined therapy) at week 12 using LOCF. A per protocol analysis was also carried out.

Comment on study design
This was a randomised double blind controlled trial. Allocation methods were described and appear adequate. While carried out in many sites, there were limited strategies for minimisation of intra- or inter-observer variability, relying on investigator meetings and analysis of results by site. Measurement of IOP is likely to have been subject to inter- and intra- patient variability owing to diurnal variation in administration and measurement of therapy, possibly diluting observed IOP lowering effects. Furthermore IOP measurement will reflect the most recent drops taken although total compliance was assessed. IOP is a surrogate measure and may not reflect visual field changes but these are difficult to assess in the paediatric population. Therapy was changed on the basis of clinical judgement as to when IOP was "uncontrolled". No indication of the IOP levels at which this was made has been provided. It is likely that different clinicians will have different thresholds both in general and in specific cases. Changes in ocular and physical examinations between visits were based on clinical judgements; photographic or other standardisation

methods were not used. The effects of this may be non-differential between treatments if the masking was satisfactory but overall may lead to unpredictable effects with under or over-recording. The sample size was based on ruling out ADRs leading to discontinuation of >25%. The choice of this cut point is arbitrary and arguably a high threshold. This study will not identify rare adverse reactions. The exclusion of patients with recent infection, inflammation or trauma < 1 month from study start appears justified as does exclusion of those with recent glaucoma procedures. Patients were allowed to have had prior therapy with any study medication or glaucoma surgery > 3 month from study start. The dose for dorzolamide was justified on the basis of the FDA request and represents the current marketed dose for those > 18 years of age. The choice of dose for the comparator was modified for those < 2 years of age taking into account data on 3 patients < 2 years of age where plasma levels were measured following topical administration and reports of apnoea in the paediatric population. The analysis strategy appears appropriate where the analysis of 'all patients as treated' will not allow dilution of safety results.

2.2.2 Results MAH trial dorzolamide vs timolol

Cohort < 2 yrs

83 patients were randomised- (56 to dorzolamide). Overall, 66 patients (79%) completed the study: 44 (53%) in the masked monotherapy phase and 22 (27%) in the open label concomitant therapy phase. The proportions of patients who discontinued from both groups were similar (10.7% v 11.1%).

Cohort ≥ 2 years but < 6yrs

101 patients were randomised- (66 to dorzolamide). Overall 81 patients (80%) in total completed the study: 61% in the masked phase and 19% in the open label phase. The proportions completing by treatment group, were similar (9.1% v 8.6%).

Treatment groups were comparable in age, gender, race and baseline IOP.

Cohort < 2 yrs

Baseline IOP was 32.6mmHg and 29.9 mmHg in dorzolamide and timolol groups respectively. Over 50% in both groups were diagnosed with congenital glaucoma. Greater numbers of patients with Sturge-Weber syndrome were randomised to dorzolamide whereas there were more patients with aphakic glaucoma in the timolol group. Similar proportions had a history of glaucoma surgery (41.1% vs 40.7%).

Cohort ≥ 2 years but < 6yrs

Baseline IOP was 28.7 mmHg and 30.3 mmHg in dorzolamide and timolol groups respectively. 57% of the dorzolamide group was diagnosed with congenital glaucoma vs 43% in the timolol group. There were more patients with aphakic glaucoma in the timolol group. Similar proportions had a history of glaucoma surgery (62.1% vs 62.9%).

Compliance was high in both groups, in both age cohorts and in both phases: mean compliance in all phases was >89% with a trend to being lowest in the open label phases.

Efficacy evaluation
Analysis of 'IOP change from baseline to week 12' was based on "all patients treated" as randomised regardless of whether patients entered the concomitant phase (overall=masked monotherapy and open label phases).

Cohort < 2 yrs
By week 12, IOP was significantly lower *overall* than baseline (mean changes of -9.4 mmHg and -9.2 mmHg in the dorzolamide and timolol groups respectively) but there was no difference between treatments for mean change in IOP : -0.25 mmHg (95% CI: -4.79 to + 4.27) or mean per cent change. Patients in the masked monotherapy only phase, showed a similar pattern although mean change in IOP was not as great in both groups: mmHg -7.3 and -7.8 mmHg dorzolamide and timolol groups respectively.

Cohort ≥ 2 years but < 6yrs
By week 12, IOP was significantly lower *overall* than baseline (mean changes of -7.6 mm Hg and -9.3 mmHg in the dorzolamide and timolol groups respectively) but there was no difference between treatment for mean change : 1.70mmHg (95% CI: -0.88 to + 4.28) or mean per cent change. Mean change in IOP for patients in the masked monotherapy phase only was similar in both groups: -7.1 mmHg and -7.4 mmHg with dorzolamide and timolol groups respectively.

Supplementary analyses were carried out by age in years. No obvious trends were identified. For US vs non US sites, the mean change in IOP appeared to be greater in non US sites for both age cohorts; baselines differences did not provide a clear explanation. No effects were identified in sub-regional/site analyses.

Inadequate control of IOP
Crude and Kaplan-Meier estimated proportions of patients discontinuing due to inadequate IOP control were high in both treatment groups and both age cohorts. The cumulative incidences are a proxy for time to failure as this depended on the visit timing.

Cohort < 2 yrs
The observed proportions of patients with inadequate control of IOP at week 12 were greater with dorzolamide than for timolol (47% v 37%) but 95% confidence intervals were wide and overlapped. Most occurred in the first three weeks of treatment.

Cohort ≥ 2 years but < 6yrs
The observed proportions of patients with inadequate control of IOP at week 12 were similar between dorzolamide and timolol (33.3% v 35.3%) and 95% confidence intervals were wide. Most occurred by the first three weeks of treatment with timolol but continued to accrue with dorzolamide.

Comment and summary
Notwithstanding the comments on study design above, this appears to be a relatively pragmatic trial with adequate control of bias. In the younger age cohort, < 2 years, dorzolamide lowered IOP by approximately 9 mmHg, and there was no obvious difference between treatments. Note that the study was not powered to show a between-treatment difference. In spite of these IOP reductions, importantly, approximately 47% of the patient population (ocular hypertension or glaucoma) were judged to be inadequately controlled on dorzolamide during this study period and

moved to concomitant therapy or out of the study. The pattern of results was similar for the 2 to <6 years age group. However, the mean change in IOP with dorzolamide from baseline was 7.6mmHg at 12 weeks; the observed proportion of those judged to be uncontrolled was slightly lower than the younger cohort 33%. Again in the 2 to <6 year group, no between-treatment differences were observed but confidence intervals were wide for differences in the outcome variables *mean change IOP* and *inadequate control of IOP*.

2.2.3 Study Design non-MSD sponsored trial dorzolamide vs brimonidine adjunctive therapy to topical beta-blockers

A further randomised controlled trial referencing dorzolamide in the paediatric population was assessed. It was submitted for a different product by a different MAH. These data are included for completeness. This trial was a three month multi-centre randomised double masked parallel comparison of the safety and efficacy of brimonidine tartrate 0.2% T.I.D. Vs dorzolamide 2% T.I.D. as adjunctive treatment to ophthalmic beta-blocker treatment in paediatric glaucoma.

Notable differences in study design between this trial and the MSD sponsored trial were:

Comparator: Brimonidine
Age group: 2-7 years inclusive
Population: Glaucoma only
Role: Adjunctive treatment to topical beta-blockers
Phase: 2 week run-in period on topical beta-blocker treatment alone
1° outcome: Within group change of IOP from baseline
2° outcome: Between group mean IOP and mean change in IOP
Sample size: 75 patients were to be randomised based on primary outcome. An ad hoc power calculation for between group comparison for non-inferiority (delta 1.5mmHg) revealed a power of 45%
IOP measurement was stated to be by hand held Tono-pen without sedation
Other variables:
Global assessment of success by investigators: 4 point scale
Patient (or guardian-rated) satisfaction: 7 point scale
Patient (or guardian-rated) comfort: 6 point scale
Biomicroscopy and ophthalmoscopy: investigators were asked to use 5 point scales

Other features of the study design

The selection of study endpoints, dose, duration of treatment and age group were justified on the basis of the FDA request. The criterion for effectiveness was a mean decrease in IOP of 3 mmHg from baseline. For patients with bilateral disease, dosing was started in the eye with more severe glaucoma and could be started in the second eye after one week. Only one eye was used in the IOP analysis. Randomisation was centrally performed and stratified by age. Treatment bottles, although 'masked' were not identical and therefore posed a risk to unmasking if showed to investigators. The pre-specified analysis plan was that safety data were based on all randomised and treated patients. All other data were based on the ITT population. A further endpoint analysis was based on IOP at 12 weeks with last observation carried forward. Changes to the analysis plan included the addition of non-parametric procedures for the analysis of IOP, additional subgroups based on age categories and a completers only analysis for IOP, with dropping of the per-protocol analysis.

2.2.4 Results of adjunctive therapy trial

38 patients were randomised to brimonidine and 38 patients to dorzolamide: 32% of patients (12/38) on brimonidine discontinued early compared to 3% of patients (1/38) on dorzolamide. Protocol deviations were similarly distributed between treatments.

Table 1. Discontinuations by treatment group

Discontinuations :	**Brimonidine**	**Dorzolamide**
Due to adverse events:	13% (5/38) somnolence, all considered drug related	3% (1/38) fever, not considered related
Lack of efficacy:	13% (5/38)	0
Other	5% (2/38)	0

No interim analyses were planned or carried out. No adjustments for multiplicity were carried out. There was no adjustment for any covariates. Data from all randomised patients were included regardless of protocol deviations. Notable protocol deviations included: completion of consent form after pre-study visit (4 patients), below inclusion weight, shorter run-in period, treatment administration time deviations, visit day deviations, visual acuity measurements could not be made, use of Goldman tonometry (3 patients), unreliability of Tono-pen measurements. One patient had no IOP data at baseline or any follow up visit and not included in any IOP analysis.

The 2 treatment groups were balanced by gender, race, iris colour, weight and height and age, distribution of ophthalmic diagnoses, use of prior adjunctive therapy (with topical beta blocker) or other medical disorders. Compliance results although measured were not summarised.

Table 2. Results primary outcome

Within group change from baseline IOP	**Brimonidine**	**Dorzolamide**
Mean baseline IOP	29.38mmHg	30.37mmHg
Mean change in IOP at week 12 from baseline2 sided paired t test	-5.29 mmHg p≤0.002	-4.41 mmHg p≤0.002
Mean change in IOP (with LOCF) at week 12	-5.16 mmHg	-5.87 mmHg

Table 3. Results secondary outcome

Between group mean change from baseline IOP	**Brimonidine vs dorzolamide**
Mean change in IOP	-0.88mm Hg (95%CI -4.58 to 2.82) between treatments. No consistent trend with one drug favoured over another
Mean change in IOP (with LOCF) at week 12	0.71(95%CI -3.33 to 4.74) p=0.728 2 sample t test 2 sided

Table 3. Results secondary outcome (cont.)

Other outcome variables	Brimonidine	Dorzolamide
Patients satisfaction: 7 point scale from v dissatisfied to v satisfied –% slightly to very satisfied	 53% (19/36)	Distribution of responses not statistically significantly different between treatments 68% (26/38) P=0.12
Patients comfort 6 point scale from soothing to intolerable: -% at baseline " at least comfortable"	 76% (29/38)	 92% (35/38)
-% at final visit " at least comfortable	84% (31/37)	79% (35/38) Suggestion of a decrease in comfort rating with dorzolamide P=0.829 between treatments
Investigators global assessment (combination of IOP efficacy, safety and tolerability on 4 point scale -% at least minimally successful	 60%(22/37)	No statistically significant difference between treatments, 76% (28/37) P=0.199

Pearson Chi sq or Fishers exact

Subgroup analyses were carried out to determine the effect of age on IOP patient comfort and investigators global assessment. There was no effect on efficacy by age. Patient comfort and global assessment by age were consistent with the overall results.

Comment and summary

Many of the comments which applied to the MSD sponsored trial also apply to this study reflecting the practical difficulties in conducting trials to assess glaucoma in general and particularly in the paediatric population. This also appears to be a relatively pragmatic trial with adequate control of bias. There are notable differences between the studies and concordance of the results would therefore not be expected. The mean change in IOP from baseline was lower in this study (approximately 5mmHg lower with dorzolamide compared to baseline, reflecting the adjunctive nature of the role of the treatment. 75% of cases treated with dorzolamide were considered at least minimally successful on the 4 point global scale assessing efficacy, safety and tolerability. No between treatment differences were statistically significant. However, the study was not powered to detect such a difference. One difference worthy of comment is that of the percentage discontinuations by treatment group, 32% of patients (12/38) on brimonidine discontinued early compared to 3% of patients (1/38) on dorzolamide, events attributable to lack of efficacy and adverse effects associated with brimonidine.

2.2.5 Medline search on efficacy

No randomised double blind trials in a paediatric glaucoma population were identified.

2.2.6 Conclusion on efficacy

Topical dorzolamide 2% T.I.D. monotherapy appears to lower IOP by 8 to 9 mmHg compared to baseline in paediatric patients with glaucoma or ocular hypertension in short term clinical studies. However a high percentage of patients, (which appears greater in the age group under 2 years compared to those aged 2 to < 6 years: 47% Vs. 33% respectively), were not considered by clinical judgement to be adequately controlled in terms of IOP.

Adjunctive treatment of topical dorzolamide 2% T.I.D. in combination with topical beta-blocker therapy appears to lower IOP in patients with paediatric glaucoma aged 2 to 6 years by an additional 5mmHg in short term studies where at least 75% were considered at least minimally successful. Longer term efficacy studies (> 12 weeks) are not available.

2.3 Cumulative review of safety

2.3.1 Dorzolamide vs timolol trial

The primary study objective was estimation of the proportion of patients discontinuing due to a drug related adverse experience.

Cohort < 2 yrs

2% of patients, initially randomised to dorzolamide, discontinued due to a drug related adverse experience. This was one case of bradycardia and attributed to concomitant timolol during the open label phase. None of 27 patients initially randomised to timolol, discontinued for a drug related adverse experience.

Table 4 Cohort < 2 yrs safety results

	Dorzolamide	**Timolol**
Discontinuations : due to Treatment related adverse events overall	2% (95% CI : 0.1% to 9.6%) n= 1/56	0% (0-12.8%) n=0/27
Adverse events masked monotherapy	75%	63%
Treatment related adverse events masked monotherapy	14%	15%
Special senses (ocular) Treatment related adverse events masked monotherapy	13%	15%
Emergent or worsening ocular symptoms	16%	26%

75% (42) of dorzolamide patients were recorded with adverse experiences, and 14% with adverse experiences considered drug related. This compares to 63% (all), and 15% (drug related) of patients treated with timolol during the masked monotherapy

phase. None of these 42 dorzolamide cases was serious and drug related. Most adverse experiences which were considered drug related, were ophthalmic. Emergent or worsening ocular symptoms occurred in 16% of dorzolamide patients vs 30% of timolol patients. Emergent or worsening ocular signs occurred in up to 12.7% with dorzolamide vs up to 12.5% with timolol (depending on ocular location). Specific dorzolamide ocular toxicity was not identified. 2% of dorzolamide patients vs 4% of timolol patients experienced a worsening visual acuity over the study period. There were no laboratory adverse experiences during this phase.

Cohort ≥ 2 years but < 6yrs

3% of patients initially randomised to dorzolamide discontinued due to a drug related adverse experience. These were due to eye pain, ocular injection, burning or itching associated with dorzolamide monotherapy. 3% of patients initially randomised to timolol discontinued for a drug related adverse experience of ocular injection.

76% of dorzolamide patients were recorded with adverse experiences with 26% considered drug related. This compares to 69% (all adverse experiences) and 23% (; drug related adverse experiences) with timolol during the masked monotherapy phase. None of these 50 dorzolamide adverse experiences was serious and drug related. Most adverse experiences which were considered drug related, were ophthalmic. Emergent or worsening ocular symptoms occurred in 27% of dorzolamide patients vs 29% of timolol patients. Emergent or worsening ocular signs occurred in up to 7.7% with dorzolamide vs up to 14.3% with timolol depending on ocular location. Specific dorzolamide ocular toxicity was not identified. 4.7% of dorzolamide patients vs 5.5% of timolol patients experienced a worsening visual acuity over the study period. Only one patient randomised to dorzolamide had a drug related adverse laboratory experience during this phase (decreased pCO2).

Table 5 Cohort ≥ 2 years but < 6yrs safety results

	Dorzolamide	Timolol
Discontinuations : due to Treatment related adverse events overall	3% (95CI 0.4 - 10.5%) n=2/66)	3% (0.1-14.9) n=1/35
Adverse events masked monotherapy	76% n=50/66	69% n=24/35:
Treatment related adverse events masked monotherapy	26% n=17/66	23% n=8/35
Special senses (ocular) Treatment related adverse events masked monotherapy	23%	17%
Emergent or worsening ocular symptoms	27%	29%

Overall there were no deaths reports on any patient randomised into the study. Mean/ Percent change in vital signs or change in alertness was minimal for dorzolamide.

Summary and comment

The upper 95% confidence limit for discontinuations attributable to dorzolamide was <11% regardless of age cohort and was associated with local ocular reactions of eye pain, burning or itching. Approximately 26% of patients were observed to experience drug related adverse effects, the majority of which were local, non serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4%, were observed to have corneal oedema or haze. Local reactions appeared similar in frequency to comparator.

2.3.2 Brimonidine vs dorzolamide trial adverse effects

A higher proportion of adverse events were recorded in the brimonidine treated group. There were also greater proportions of i) discontinuations due to adverse effects and ii) adverse drug reactions (ADRS) considered brimonidine-treatment related compared to dorzolamide.

Table 6 safety results

	Brimonidine	**Dorzolamide**
Adverse events	89% (33/38)	66% (25/38)
Discontinuations : due to adverse events	13% (5/38) somnolence, all considered drug related	3% (1/38) fever, not considered related
Special senses- all	16% (6/38)	37% (14/38)
Treatment related adverse events	66% (25/38)	26% (10/38)

The only severe and /serious adverse events in the dorzolamide group were fever and otitis media considered unrelated to treatment. There were no deaths. With dorzolamide, treatment related adverse effects occurring in 2 or more patients included burning sensations in the eye (7.9%) and corneal filaments (5.3%). No differences between treatments were observed in terms of change in visual acuity, biomicroscopy, ophthalmoscopy or vital signs. The most obvious difference between treatments was the occurrence of somnolence with brimonidine.

2.3.3 Spontaneous data

The MAH provided an analysis of the company database for spontaneous reports of adverse events with dorzolamide in patients < 18 years from time of product launch (Nov 1994) through to May 2004. 26 reports were identified, from health professionals or regulatory authorities including 8 serious reports. The company stratified the analysis into those < 6 years and those 6 to < 18 years.

There were 9 reports in those < 6 years. Reports were as follows:

Table 7 spontaneous reports in patients < 6 years

Reaction	**Age at event**	**MAH comment**	**Assessor's comment**
Skin irritation	24 weeks old	Labelled	
Ocular burning	19 weeks old	Labelled	
Corneal clouding	6 months old	Unlikely	Agree (negative rechallenge)
Lethargy, hypotension and hypothermia (serious)	4 week old	Also taking brimonidine: likely suspect	Agree
Metabolic acidosis (serious)	5 day old	Not likely: renal immaturity	Disagree: possible: positive de-challenge See Annex 4 [page 75]

Metabolic acidosis (serious)	4 week old	Difficult to assess	Difficult to assess but possible
Shallow breathing, hyperventilation and respiratory acidoisis	5 day old prem	Also taking oral Carbonic anhydrase	Unlikely
Overdose: somnolent	8 month old	Unlikely	Possible
Overdose: dehydration	2 year old	Difficult to assess	Difficult to assess

Assessor's comment
Whilst disturbances in acid base balance are a recognised adverse reaction with oral carbonic anhydrase inhibitors, the MAH states in the SPC that these have not been associated specifically with dorzolamide. There is a signal of metabolic acidosis in the very young particularly with renal immaturity/impairment. This is plausible when the primary route of elimination is unchanged though the urine.

Children 6 to <18 years old
17 reports were analysed in patients in this age group.

7 reports were local and non serious.
There were no apparent signals in this category

3 reports were local and systemic non-serious
No signals were apparent.

7 reports of systemic averse effects
(2 serious)
Case 1: headache and nausea
Case 2: nausea, abdominal pain and watery stools
No new signals were apparent in this group.

(5 non serious systemic)
Case 1: crystals in urine
Case 2: nephrolithisais
Case 3: changes in nail growth
Case 4: depression
Case 5: dizziness and decreased blood pressure
No new signals were apparent in this group

2.3.4 Medline search
A search of Medline revealed the publication of a case of metabolic acidosis in a 5 day old.

2.3.5 Conclusion on safety
Clinical studies in a limited number of paediatric patients indicated that the majority of adverse reactions were local and non serious. The upper 95% confidence limit for discontinuations attributable to dorzolamide was <11% regardless of age cohort and was associated with local ocular reactions of eye pain, burning or itching. Approximately 26% of patients were observed to experience drug related adverse

effects, the majority of which were local, non serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4%, were observed to have corneal oedema or haze. Local reactions appeared similar in frequency to comparator. These studies were not large enough to detect rare adverse reactions. There is a signal from spontaneous reports of metabolic acidosis in the very young.

2.4 Overall conclusion

The product information should be updated to reflect conclusions of efficacy and safety as above.

The product information should be updated to reflect conclusions of efficacy and safety as above. In particular, there are data to support use of topical dorzolamide 2% as adjunctive therapy to beta-blockers in paediatric glaucomas, although the dose used was T.I.D. (adult dose is B.D.)

The adult indication for dorzolamide is for monotherapy *as second line* in patients unresponsive to beta-blockers or in whom beta-blockers are contra-indicated in the treatment of ocular hypertension, open angle glaucoma and pseudo-exfoliative glaucoma. With regard to monotherapy in children, it could be argued that the data in children at least support monotherapy as second line, and may justify use as first line monotherapy in the short-term topical treatment of ocular hypertension or glaucoma with dorzolamide 2% in the paediatric population.

There should be a contra-indication in those < 36 weeks gestational age and < 1 week of age or with significant renal tubular immaturity

2.4.1 CONCLUSIONS AND RECOMMENDATIONS OF THE CSM PAEDIATRIC MEDICINES WORKING GROUP

The Working Group concluded that the risk benefit appeared favourable for the use of topical dorzolamide 2% in the treatment of congenital/paediatric glaucomas on the basis of the data presented. The group noted that the risk of metabolic acidosis in association with use of dorzolamide in the very young should be weighed against the potential benefit of treatment. The group noted that the comparators used in the trials were also not licensed for use in children and the problem that this posed for specifying the therapeutic indications as second line monotherapy use or use as an adjunctive agent. The group noted that the licensed dose of dorzolamide as adjunctive therapy for adults was twice a day and that the dose used in the trials was three times a day. The group agreed that the recommended dose for adjunctive therapy for paediatric use should be three times a day.

This group recommended that the MAH should submit a variation to the Reference Member State in line with the following proposed changes to the SPC and PIL. The group agree that the assessment report on the safety and effectiveness of dorzolamide in paediatric glaucoma, should be published on the MHRA website.

Recommended changes to the Summary of product characteristics

Section 4.1 Therapeutic indications

Add

- “in the short term treatment of paediatric glaucomas as adjunctive therapy and for monotherapy when other treatments have proved ineffective or are unsuitable.”

Section 4.2 Posology and method of administration
Paediatric use:
Add “see Sections 4.1, 4.4, 4.8 and 5.1. The dose of dorzolamide in adjunctive therapy for paediatric glaucoma is three times a day.”
Delete “safety and effectiveness in children have not been established”

Section 4.4 Special warnings and special precautions for use
Add “Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. Patients with significant renal tubular immaturity should only receive dorzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis.

Section 4.8 undesirable effects
Add “In small short term clinical trials, approximately 26% of paediatric patients were observed to experience drug related adverse effects, the majority of which were local, non serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4%, were observed to have corneal oedema or haze. Metabolic acidosis in association with dorzolamide has been observed in patients under 2 months of age; in which case, treatment with dorzolamide should be discontinued.

Section 5.1 Pharmacodynamic properties
Clinical effects
Add “Topical dorzolamide 2% T.I.D. monotherapy appears to lower IOP by 8 to 9 mmHg **[NOTE PLEASE ADD 95% CONFIDENCE INTERVALS AND RESULTS STRATIFIED BY AGE GROUP]** compared to baseline in paediatric patients with glaucoma or ocular hypertension in short term clinical studies. However a high percentage of patients, (which appears greater in the age group under 2 years compared to those aged 2 to < 6 years: 47% Vs. 33% respectively **ADD 95% CONFIDENCE INTERVALS**), were not considered by clinical judgement to be adequately controlled in terms of IOP during these studies.
Adjunctive treatment of topical dorzolamide 2% T.I.D. in combination with topical beta-blocker therapy appears to lower IOP in patients with paediatric glaucoma aged 2 to 6 years, by an additional 5mmHg compared to baseline in short term studies.

Longer term efficacy studies (> 12 weeks) are not available.”

b) PIL
The PIL should be modified in line with the proposed SPC changes.